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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/714,447
Filing Date: November 17, 2003
Appellant(s): ROBERTS ET AL.

Jacqueline M. Cohen
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/3/07 appealing from the Office action mailed 2/16/06.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellants' statement of the grounds of rejection to be reviewed on appeal is substantially correct. With regard to the 103 rejection, the examiner only relied on **3** NPL references, namely the earlier Calderon reference (ref. C4) published in 1994 and the 2 Bilsky refernces (ref. C1 and C2). The remaining Calderon reference (ref. C5) was published in 1997 after applicants' international filing date and thus is not competent.

The rejection over US 6,696,447 on the grounds of obviousness-type double patenting has been overcome by the Terminal Disclaimer filed on 12/3/07 which has been approved. Thus, the only ground of rejection is the 103 rejection set forth below.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

US 5,658,908

Calderon et al. J.Med. Chem. vol.37, pp.2125-2128 (1994).

Bilsky et al. Reg. Peptides vol.54, pp.25-26 (1994).

Bilsky et al. J.Pharmacol. Exper. Ther. vol.273,pp.359-366 (1995).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Calderon (ref. C4) and Bilsky references (refs. C1 and C2) in view of Chang (US'908). As US Chang is the equivalent of WO'062, the WO document is not being relied on herein. Also, as the present case is a refiled case of 2 earlier patents originally presented as paper files, copies of all applied NPL documents have been provided in the instant electronic file.

Each of the primary references teach very similar compounds to that claimed herein for treating pain (i.e. having antinociceptive activity) based on activity at one or more opioid receptors, namely μ, and δ. In Calderon see compounds 8 and 9 in reaction scheme 2 and a discussion on page

2126, right column, of their activity as being highly selective at the δ receptor which is a desirable advantage as it minimizes physical dependence while promoting antinociceptive activity. Also see OH analogs 1 and 10 which are stated to be selective towards the δ receptor. In Bilsky, ref. C1 and C2 see anisole derivatives, SNC80 and SNC 67 which are the same compounds (i.e. 8 and 9) discussed in Calderon.

While compounds in the primary references are no longer anticipatory in view of the deletion of allyl as a choice at instant R1, and the presence of only hydrogen on piperazino carbons, the compounds in the primary references are obvious variants of that still claimed herein since the differences allyl vs instant R1 as H, alkyl, aralkyl etc. are taught as interchangeable as well as methyl and hydrogen on piperazino carbons in similar compounds having the same use as described by the Chang patent. Note in Chang the definition of R3-R5 which can be either H or Me and the choices for R6 which include hydrogen, alkyl, cycloalkyl, aralkyl in col.2 of the US patent. Note that these substituents are within the preferred embodiments taught in col.6 as well as in numerous other columns pointed out by appellants in the Brief as further discussed below. Additionally, the thrust of Chang's invention is to develop highly selective opioid agonists as

discussed in cols.17-18 and in the background section and delta agonists are included. See col.20 which includes instant compounds (i.e. where Y group is para-substituted on the phenyl ring) that are explicitly taught as being delta agonists. Thus it would have been obvious to one skilled in the art at the time the instant invention was made to replace the aforementioned groups in the primary references with those present herein at instant R1 and R3-R6 and in so doing obtain additional compounds for treating pain in view of the equivalency teachings outlined above in the secondary reference.

Appellants' traverse is not persuasive. On p.5 of the Brief penultimate paragraph, it is stated that Calderon stresses the importance of using dimethyl substitution so that chirality is present on the piperazine ring . This is not entirely accurate. What Calderon is saying in the "Chemistry" section is that one needs a chiral precursor to make a chiral final product. This is of course a reasonable statement to make but is not the same thing as saying one needs dimethylated piperazines in order to be able to have the desired activity. In fact results of structure- activity data for various enantiomer pairs led Calderon to conclude that configuration at the benzylic carbon is the "most important sterochemical determinant of δ receptor

binding selectivity". See last few lines in the right column of p.2126. Appellant's claim includes not only racemic compounds but also individual stereoisomers and thus would include compounds having the same absolute configuration at the carbon atom linking the piperazine ring to the 2 phenyl rings. With regard to the Chang reference, the examiner totally disagrees with appellant's assertion that H and Me are **not** as taught as interchangeable and H is not within the preferred embodiment. This argument is not new but was raised in an earlier action. The passages appellants points to in Chang **include** H as well as Me. Note the wording in the preferred R3-R5 choices throughout the patent is literally saying **no more than** 2 R groups can be Me. This is consistent with the claims which include a proviso forcing one of R3-R5 to be Me. If appellants' interpretation was correct, then the proviso would not have been needed in claim 1 of US Chang since the same language otherwise appears there that appears in col.6 and elsewhere. The proviso was added to exclude any H's on these R groups to avoid prior art. Also, contrary to what appellants assert, there are species described in the patent that lack methyl groups on the piperazine carbons. See species #3 and #4 in col.7. It is well settled that a reference is not limited to its preferred embodiments or

working examples but for all that it fairly teaches. See In re Lamberti 192 USPQ 278; In re Mills 176 USPQ 196:In re Burckel 201 USPQ 67 regarding the latter point. However as discussed above the embodiments claimed herein are within the preferred embodiments taught by Chang.

Appellants' additional arguments that "Chang teaches away" from demethylated piperazines in view of the prosecution history conducted in Chang prior to issuance of the patent is noted but not agreed with. The Declaration presented in Chang was a comparative showing between prior art and relevant compounds of Chang that are totally dissimilar to that shown as obvious herein. There is no carboxamide substituent on the phenyl ring always required herein. The quote in the Declaration and elsewhere in Chang's remarks appellants heavily rely on as showing a general trend of better activity when at least one methyl group is present, is noted, but is believed to be taken out of context and its significance to the present claimed subject matter exaggerated given the homogeneity of the tested examples along with their dissimilarity to the compounds on appeal herein. Thus it is not seen how the declaration in Chang mitigates its teachings as a reference. A fairly recent decision, In re Gurley 31 USPQ2d 1130 is worth noting. It also dealt with a purported "teach away" situation in

which the Court agreed that such was present in the prior art (Yamaguchi) but said this: "Gurley's position appears to be that a reference that "teaches away" can not serve to create a *prima facie* case of obviousness. We agree that this is a useful general rule. However, such a rule can not be adopted in the abstract, for it may not be applicable in all factual circumstances. Although a reference that teaches away is a significant factor to be considered in determining unobviousness, the nature of the teaching is highly relevant, and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use".

Appellants further rely on the recent Takeda decision to bolster their position but that case differs considerably in its facts from herein. The prior art compound relied on by the examiner in that case was documented in more than one reference and by expert witnesses as having serious side-effects that would be deleterious for its intended purpose. There is no such evidence herein. Additionally, the "lead" prior art compound in Takeda was not particularly singled out for its activity in the reference relied on by the examiner, which the Court stated "discloses hundred of millions of TZD compounds". The primary references relied on herein are directed to a very

narrow scope of compounds as either racemic or enantiomers, with particular emphasis on the high delta receptor selectivity for one or more enantiomers. It is further noted that the Court in Takeda relied on the unexpectedly superior properties of appealed compound over compound b. Thus given the totality of the facts in Takeda, the decision rendered was based on "reasonable expectation" of success in performing the intended use, which in that case led to disqualification of the prior art compound.

Thus, in the present situation given the finite number of compounds pointed out in the primary reference for modification and the need to find more selective delta agonists, the examiner believes that the burden set forth in the KSR decision has been met.

Additionally, appellants are in a poor position to argue for separate patentability of instant R^1 groups vs. allyl as well as H vs. Me on piperazino carbons as all have been originally presented as equivalents for purpose of practicing the invention. Note In re Skoll 187 USPQ 481 regarding the latter point.

(10) Response to Argument

The response has been included with the rejection above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Emily Bernhardt/

Primary Examiner, Art Unit 1624

Conferees:

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